Atty. Dkt. No. 081356-0153

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Yasuhiko KOEZUKA et al

Title: METHOD FOR ACTIVATING HUMAN ANTIGEN PRESENTING CELLS, ACTIVATED HUMAN ANTIGEN - PRESENTING CELLS, AND USE THEREOF

Appl. No.: 09/721,768

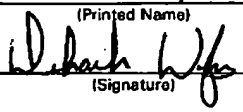
Filing Date: 11/27/2000

Examiner: Leigh C. Maier

Art Unit: 1623

CERTIFICATE OF FACSIMILE TRANSMISSION
I hereby certify that this paper is being facsimile transmitted to the United States Patent and Trademark Office, Alexandria, Virginia at (703) 872-9306 on the date below.

Deborah Wykes
(Printed Name)


(Signature)

June 20, 2003
(Date of Deposit)

AMENDMENT TRANSMITTAL

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Sir:

Transmitted herewith is an amendment in the above-identified application.

[ ] Small Entity status under 37 C.F.R. § 1.9 and § 1.27 has been established by a Small Entity statement previously submitted.

[ ] Small Entity statement is enclosed.

[X] The fee required for additional claims is calculated below:

	Claims as Amended		Previously Paid For		Extra Claims Present		Rate		Additional Claims Fee
Total Claims:	40	–	23	=	17	x	$18.00	=	$306.00
Independents:		–	3	=	0	x	$84.00	=	$0.00
First presentation of any Multiple Dependent Claims:						+	$280.00	=	$280.00
							CLAIMS FEE TOTAL:	=	$586.00

Atty. Dkt. No. 081356-0153

[X] Applicant hereby petitions for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

[ ]	Extension for response filed within the first month:	$110.00	$0.00
[ ]	Extension for response filed within the second month:	$410.00	$0.00
[X]	Extension for response filed within the third month:	$930.00	$930.00
[ ]	Extension for response filed within the fourth month:	$1,450.00	$0.00
[ ]	Extension for response filed within the fifth month:	$1,970.00	$0.00
	EXTENSION FEE TOTAL:		$930.00
[ ]	Statutory Disclaimer Fee under 37 C.F.R. 1.20(d):	$110.00	$0.00
	CLAIMS, EXTENSION AND DISCLAIMER FEE TOTAL:		$1516.00
[ ]	Small Entity Fees Apply (subtract ½ of above):		$0.00
	TOTAL FEE:		$1516.00

[X] Please charge Deposit Account No. 50-0872 in the amount of $1516.00. A duplicate copy of this transmittal is enclosed.

[ ] A check in the amount of $1516.00 is enclosed.

[X] The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Atty. Dkt. No. 081356-0153

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date June 20, 2003

By

FOLEY & LARDNER
Customer Number: 22428
22428
PATENT TRADEMARK OFFICE
Telephone: (858) 847-6717
Facsimile: (858) 792-6773

Richard San Pietro
Reg. No. 45,071
For Stephen A. Bent
Reg. No. 29,768

Atty. Dkt. No 081356-0153

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Yasuhiko KOEZUKA et al

Title: METHOD FOR ACTIVATING HUMAN ANTIGEN PRESENTING CELLS, ACTIVATED HUMAN ANTIGEN - PRESENTING CELLS, AND USE THEREOF

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CERTIFICATE OF FACSIMILE TRANSMISSION
I hereby certify that this paper is being facsimile transmitted to the United States Patent and Trademark Office, Alexandria, Virginia at (703) 872-9306 on the date below.

Deborah Wykes
(Printed Name)

(Signature)

June 20, 2003
(Date of Deposit)

PETITION FOR EXTENSION OF TIME

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Sir:

Applicant hereby petitions the Commissioner under 37 C.F.R. §1.136(a) for a three-month extension of time for response in the above-identified application for the period required to make the attached response timely.

The extension fee for response within the third month is $930.00. Please charge our Deposit Account No. 50-0872 for this amount.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed

Atty. Dkt. No 081356-0153

herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872.

Respectfully submitted,

Date June 20, 2003

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Applicant: Yasuhiko KOEZUKA *et al.*

Title: METHOD FOR ACTIVATING HUMAN ANTIGEN PRESENTING CELLS, ACTIVATED HUMAN ANTIGEN - PRESENTING CELLS, AND USE THEREOF

Appl. No.: 09/721,768

Filing Date: 11/27/2000

Examiner: Leigh C. Maier

Art Unit: 1623

AMENDMENT

Commissioner for Patents
Alexandria, Virginia 22313-1450

Sir:

Introductory Comments

This communication is responsive to the Office Action dated December 23, 2003, concerning the above-referenced patent application. Applicant has enclosed with this amendment a Petition for Extension of Time to make this response timely.

Atty. Dkt. No. 081356-0153

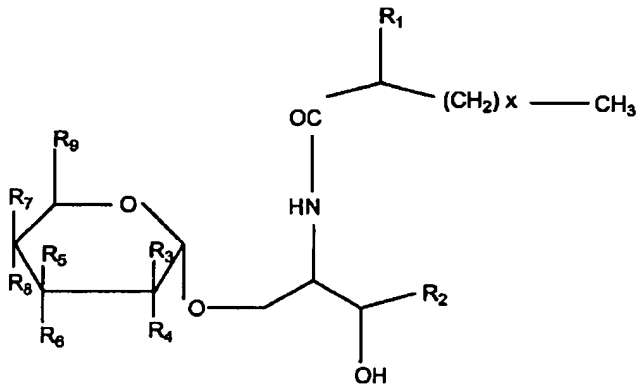
Amendments to the Claims

Please amend the application as follows:

Please cancel claims 1-13 and 20-21. Please add claims 24 – 44 as follows.

1-23 (Cancelled)

24. (New) A method for activating a human antigen-presenting cell, comprising culturing human dendritic cells in vitro with at least one of the glycoside compounds represented by formula (A) or salts thereof and a tumor antigen:



(A)

wherein

R_1 is H or OH;

X is an integer of from 7 to 25;

R_2 is a substituent defined by any one of the following (a) to (e):

(a) $-CH_2(CH_2)_YCH_3$;

(b) $-CH(OH)(CH_2)_YCH_3$;

(c) $-CH(OH)(CH_2)_YCH(CH_3)_2$;

(d) $-CH=CH(CH_2)_YCH_3$; and

(e) $-CH(OH)(CH_2)_YCH(CH_3)CH_2CH_3$

wherein Y is an integer of from 5 to 17;

R_3 is H;

R_4 is OH;

R_5 is OH;

R_6 is H;

one of R_7 and R_8 is H and the other is OH; and

R_9 is H, CH_3 or CH_2OH.

25. (New) The method of claim 24, wherein the human dendritic cells are obtained by culturing human monocytes in vitro in the presence of GM-CSF and IL-4.

26. (New) The method of claim 25, wherein the human monocyte is prepared from human peripheral blood.

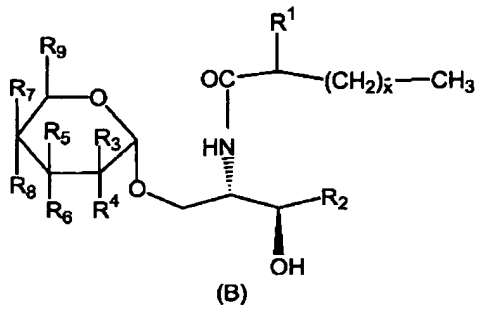
27. (New) The method of claim 25, wherein the human monocyte is prepared from human umbilical cord blood.

28. (New) The method of claim 25, wherein the human monocyte is prepared from a human bone marrow cell.

29. (New) The method of claim 25, wherein the human monocyte is prepared from human epidermis.

Atty. Dkt. No. 081356-0153

30. (New) The method of claim 24 or 25, wherein the glycoside compound is a compound represented by formula (B):



(B)

wherein:

R_1 is H or OH;

X is an integer of from 7 to 25;

R_2 is a substituent defined by any one of the following (a) to (e):

(a) $-CH_2(CH_2)_YCH_3$;

(b) $-CH(OH)(CH_2)_YCH_3$;

(c) $-CH(OH)(CH_2)_YCH(CH_3)_2$;

(d) $-CH=CH(CH_2)_YCH_3$; and

(e) $-CH(OH)(CH_2)_YCH(CH_3)CH_2CH_3$

wherein Y is an integer of from 5 to 17;

R_3 to R_9 are substituents defined by any one of the following (i) to (ii):

(i) R_3, R_6 and R_8 are each H;

R_4 is OH;

R_5 is OH;

R_7 is OH; and

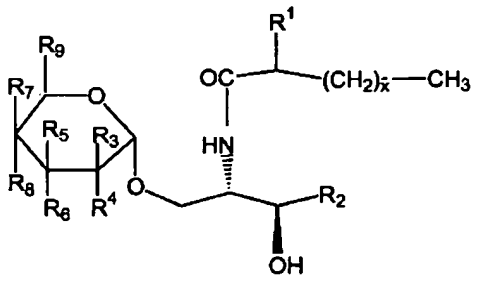
R_9 is H, CH_3, or CH_2OH;

(ii) R_3, R_6 and R_7 are each H;

R_4, R_5 and R_9 are as defined as in (i); and

R_8 is OH.

31. (New) The method of claim 24 or 25, wherein the glycoside compound is a compound represented by formula (B):



(B)

wherein:

R_1 is H or OH;

X is an integer of from 7 to 25;

R_2 is a substituent defined by any one of the following (a) to (e):

(a) $-CH_2(CH_2)_YCH_3$;

(b) $-CH(OH)(CH_2)_YCH_3$;

(c) $-CH(OH)(CH_2)_YCH(CH_3)_2$;

(d) $-CH=CH(CH_2)_YCH_3$; and

(e) $-CH(OH)(CH_2)_YCH(CH_3)CH_2CH_3$

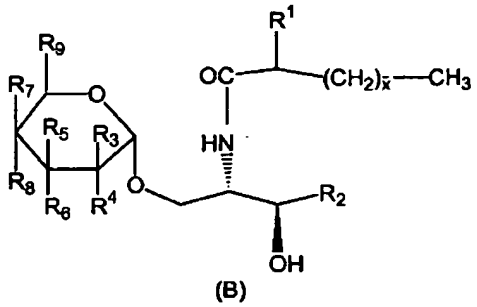
where Y is an integer of from 5 to 17;

R_3, R_6, and R_8 are each H;

R_4, R_5, and R_7 are each OH; and

R_9 is CH_2OH.

32. (New) The method of claim 24 or 25, wherein the glycoside compound is a compound represented by formula (B):



(B)

wherein

R_1 is H or OH;

X is an integer of from 7 to 25;

R_2 is a substituent defined by any one of the following:

(b) $-CH(OH)(CH_2)_YCH_3$;

(c) $-CH(OH)(CH_2)_YCH(CH_3)_2$; and

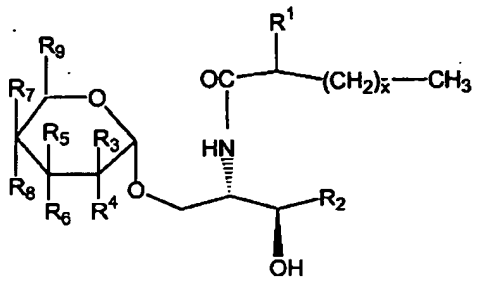
(e) $-CH(OH)(CH_2)_YCH(CH_3)CH_2CH_3$; wherein Y is an integer of from 5 to 17; and

R_3, R_6 and R_8 are each H;

R_4, R_5 and R_7 are each OH; and

R_9 is CH_2OH.

33. (New) The method of claim 24 or 25, wherein the glycoside compound is a compound represented by formula (B):



(B)

wherein

X is an integer of from 7 to 25;

R_1 is H;

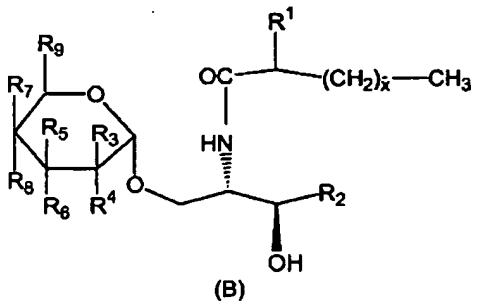
R_2 is $-CH(OH)(CH_2)_YCH_3$ where Y is an integer of from 5 to 17;

R_3, R_6 and R_8 are each H;

R_4, R_5 and R_7 are each OH; and

R_9 is CH_2OH.

34. (New) The method of claim 24 or 25, wherein the glycoside compound is a compound represented by formula (B):



(B)

wherein

X is an integer of from 7 to 25;

R_1 is H;

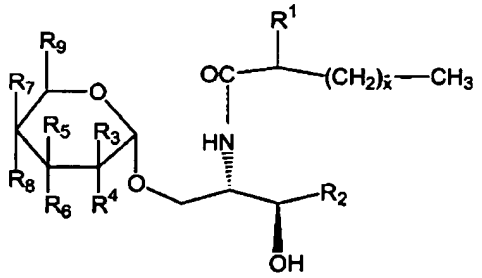
R_2 is $-CH(OH)(CH_2)_YCH_3$ where Y is an integer of from 5 to 17 and where the OH group is of R configuration; and

R_3, R_6 and R_8 are each H;

R_4, R_5 and R_7 are each OH; and

R_9 is CH_2OH.

35. (New) The method of claim 24 or 25, wherein the glycoside compound is a compound represented by formula (B):



(B)

wherein

X is from 21 to 25 and Y is an integer of from 11 to 15;

R_1 is H;

R_2 is $-CH(OH)(CH_2)_YCH_3$ where Y is an integer of from 5 to 17 and where the OH group is of R configuration; and

R_3, R_6 and R_8 are each H;

R_4, R_5 and R_7 are each OH; and

R_9 is CH_2OH.

36. (New) The method of claim 24 or 25, wherein the glycoside compound is selected from the group consisting of:

(2S, 3S, 4R)-1-(α-D-galactopyranosyloxy)-2-hexacosanoylamino-3,4-octadecanediol;

(2S, 3R)-1 -(α-D-galactopyranosyloxy)-2-[(R)-2-hydroxytetracosanoylamino]-3-octadecanol;

(2S, 3R)-1 -(α-D-galactopyranosyloxy)-2-tetracosanoylamino-3-octadecanol;

(2S, 3R)-1-(6'-deoxy-α-D-galactopyranosyloxy)-2-tetracosanoylamino-3-octadecanediol;

(2S, 3S, 4R)-1-(α-D-galactopyranosyloxy)-2-[(R)-2-hydroxytetracosanoylamino]-3,4-octadecanediol; and

(2S, 3S, 4R)-1-(α-D-galactopyranosyloxy)-2-tetracosanoylamino-3,4-octadecanediol.

37. (New) The method for activating human antigen-presenting cell of any one of claims 24-29, wherein the tumor antigen is associated with melanoma.

38. (New) The method for activating human antigen-presenting cell of claim 30, wherein the tumor antigen is associated with melanoma.

39. (New) The method for activating human antigen-presenting cell of claim 31, wherein the tumor antigen is associated with melanoma.

40. (New) The method for activating human antigen-presenting cell of claim 32, wherein the tumor antigen is associated with melanoma.

41. (New) The method for activating human antigen-presenting cell of claim 33, wherein the tumor antigen is associated with melanoma.

42. (New) The method for activating human antigen-presenting cell of claim 34, wherein the tumor antigen is associated with melanoma.

43. (New) The method for activating human antigen-presenting cell of claim 35, wherein the tumor antigen is associated with melanoma.

44. (New) The method for activating human antigen-presenting cell of claim 36, wherein the tumor antigen is associated with melanoma.

Remarks

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons which follow.

The examiner rejects Claims 1-10 under 35 U.S.C. 102 (b) over MORITA et al. Claim 24 recites a method for activating human antigen-presenting cells by culturing human dendritic cells (DCs) *in vitro* with at least one of the glycoside compounds recited in the claim (or salts thereof), and a tumor antigen. Claim 25 adds the limitation that the human dendritic cells are obtained by culturing human monocytes *in vitro* in the presence of GM-CSF and IL-4 (hereinafter referred to as monocyte-derived DCs).

As the present application states, at page 2, line 21 – page 3, line 6, Sallusto *et al., J. Exp. Med.* 179: 1109 (1994) (attached), disclose that monocytes are differentiated into dendritic cells when cultured in the presence of GM-CSF and IL-4. In keeping with claim 25, therefore, human dendritic cells may be obtained by culturing human monocytes in vitro in the presence of GM-CSF and IL-4.

Pharmacological tests 9, 10, and 12 of the specification teach that activated dendritic cells are obtained by culturing human monocyte-derived DCs with KRN7000, which is one of the glycoside compounds recited in claim 24. Pharmacological test 8 teaches that murine spleen-derived dendritic cells (DCs) are cultured with KRN7000 and a tumor antigen. Pharmacological test 3 teaches that antigen-presenting cells derived from murine spleen mainly contain dendritic cells. Accordingly, the amendment does not include new matter.

The Morita reference does not disclose or suggest the salient features of the recited methods. Morita fails to disclose any method of activating human antigen-presenting cells

by culturing dendritic cells with a glycoside compound of the claims and a tumor antigen. Accordingly, Morita does not anticipate the presently claimed invention.

Claims 11 and 13 stand rejection under 35 U.S.C. 103(a) over MORITA *et al.* in view of KOEZUKA *et al.* and HSU *et al.* This rejection is respectfully traversed.

As explained above, MORITA *et al.* neither discloses nor suggests a method for activating human antigen-presenting cell by culturing human dendritic cells *in vitro* with a glycoside compound and a tumor antigen. KOEZUKA does not compensate for this failing.

According to the specification (page 2, lines 13-20), it was reported that DCs derived from murine bone marrow cultured with a tumor antigen elicit tumor immunity. HSU *et al.* also describes the effect of APCs exposed to a conjugate of GM-CSF linked to a tumor antigen. It was recognized that APCs treated by a tumor antigen induce antigen specific cytotoxic T-lymphocyte (CTL) activity. On the other hand, at the priority date of the present application, the inventors (including KOEZUKA) never thought that KRN7000 per se was presented on DCs. It was only after the priority date of the present application that the mechanism underlying the induction of anti-tumor activity of DCs treated by KRN7000 was revealed. It is known that KRN7000 is presented by a CD1d molecule on DCs and the KRN7000-presented DCs are recognized by other immunocompetent cells (Vα24NKT cells in humans, Vα14NKT cells in mice) and the NKT cells induce (antigen)-nonspecific anti tumor activity.

Thus, it was not understood that DCs treated with a combination of KRN7000 and a tumor antigen had synergistic anti tumor activity. By the same token, the person of ordinary skill found no motivation to treat DCs with both KRN7000 and a tumor antigen.

Furthermore, the prior art was uninformed that a synergistic anti-tumor effect could be achieved by treating DCs with a combination of KRN7000 and a tumor antigen.

Pharmacological test 8 of the present application demonstrates that mouse dendritic cells cultured with KRN7000 together with a tumor antigen provide a strong tumor growth-inhibitory effect. As shown in Figure 9, little or no tumor growth-inhibitory effect was observed when DCs pretreated with vehicle and tumor antigen (V-T-APC) or DCs pretreated with vehicle (V-APC) were injected. On the contrary, as Pharmacological test 8 describes, DCs pretreated with KRN7000 and a tumor antigen (KRN-T-APC) produced a more remarkable tumor growth inhibitory effect than DCs pretreated with KRN7000 (KRN-APC). Therefore, the treatment of DCs with KRN7000 and a tumor antigen has a synergistic effect on enhancing tumor inhibitory activity of DCs. Consequently, since the prior art does not describe human deridritic cells treated with the glycoside compound in the presence of a tumor antigen, nor that the methods of the present claims have advantageous and unexpected effects over the prior art, the claims are not obvious over the cited references.

The Examiner also states that Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over MORITA as applied to claims 1-10 above, in view of KOEZUKA et al. and HSU et al., as applied to claims 1-11 and 13 above, and further in view of O'DOHERTY et al.

Claim 12 is directed to a method of using MCM. However, the present claims do not include claims directed to a method using MCM. Accordingly, the reason for rejection of claim 12 is obviated.

Atty. Dkt. No. 081356-0153

Conclusion

After amending the claims as set forth above, claims 24-44 are now pending in this application.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Date June 20, 2003

Respectfully submitted,

Stephen A. Bent
FOLEY & LARDNER
Suite 500
3000 K Street, N.W.
Washington, DC 20007-5109
Telephone: (202) 672-5300

By _____
Richard San Pietro
Reg. No. 45,071
For Stephen A. Bent
Reg. No. 29,768